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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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FOLEY,S	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/043,933	BALLOUL ET AL.	
	Examiner	Art Unit	
	Shanon A. Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-20,25-31 and 38-78* is/are pending in the application.

4a) Of the above claim(s) *10-20,25-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Response to Amendment

In response to the previous Office Action in paper no. 18, 10/6/00, the Applicant has cancelled all of the previously examined claims, 1-9, 21, 23, 24, and 32-37. Claims 10-20 and 25-31 remain withdrawn from consideration due to a non-elected invention. New claims, 38-78 are added and are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 38 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment filed 1/8/00 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: claim 38 is now directed to at least one early polypeptide and one late polypeptide from the papillomavirus with the specific exception of E7 and L2 combination. This negative limitation cannot be found in the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 39-41, 48-50, 55-57, 64-66, 71, and 72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nononcogenic variant of E6 having amino acids 111-115 deleted and a nononcogenic variant of E7 having amino acids 21-26 deleted, does not reasonably provide enablement for any polypeptide variant that has 75% sequence homology with E6 and E7. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to pharmaceutical compositions containing polypeptides of the papillomavirus that have a degree of similarity of at least 75% sequence homology with E6, E7, L1, and/or L2 proteins. The specification does not teach all of "residues involved in the process of transformation of the infected cell" (page 4, line 37 to page 5, line 6). Nor does the specification teach all of the possible combinations of structural elements within the peptides that are involved with transformation of the infected cell that could be altered 25% and still maintain the ability to treat papilloma infections. The specification teaches a single species for a non-oncogenic form of E6 that has deletions in the amino acids at positions 111-115 and a non-oncogenic form of E7 that has deletions in the amino acids at positions 21-26.

The state of the prior art at the time the invention was made teaches that the amino acid sequences for E7 to form the complex formation with retinobastoma (RB) tumor suppressor gene is located at a small stretch of amino acids surrounding the cysteine residue at sequence position 24, see Munger et al. in the last 2 sentences of the introduction on page 4099. The state of the art at the time the invention was made teaches that an amino acid mutation in E6 reduces binding to p53 by 94% by deleting amino acids 111-115, see Crook et al. in the last paragraph of column 1

on page 547. The teachings in the prior art do not enable one skilled in the art an ability to predict other regions within E6 or E7 that are involved in the process of transformation of the infected cell. Therefore, it is not possible to predict which mutations in which region of the polypeptides can be made in order to make and use the claimed invention.

The genus of the claimed invention encompasses a wide variety of possible derivatives, variants, or fragments of each polypeptide and the single species of each polypeptide that is taught in the specification is not seen as representative for the full genus claimed. Therefore, due to the broad scope of the claims, the state of the prior art at the time of the invention, the inability of the skilled artisan to predict what other regions within the polypeptide are involved in the process of transformation, the lack of direction and guidance provided by the inventor, and the limited existence of working examples, undue experimentation would be required of one skilled in the art to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

Claim Rejections - 35 USC § 103

The previous Office action rejected claims 1-5, 8, 9, 21, 23, and 24 in a 102(b) rejection by Stanley et al. in WO 96/29091. The rejection should have been made over 102(a).

Claims 38-50, 58-60, 62-66, 74-76, and 78 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Stanley et al. in WO 96/29091.

The claims are drawn to administering a pharmaceutical composition that comprises at least one polypeptide from the early region and at least one polypeptide from the late region that

has 75% homology to E6, E7, L1, or L2 and an immunostimulatory peptide in order to treat or prevent papillomavirus tumors from specific HPV types.

Stanley et al. teaches a papillomavirus vaccine for the treatment of human papillomavirus infection, see page 4, lines 6-7 and 17-22. The composition comprises at least a substantial part of one of the proteins E1, E2, E4, E6, E7, L1 and/or L2 of HPV types 6, 11, 16, and/or 18, and IL-12, see page 4, lines 29-37, and claims 5, 6, 13, 15. Claim 3 further anticipates the use of IL-12 as an immunostimulatory vaccine adjuvant, which anticipates the claim limitations in the instant application that are directed to the composition comprising immunostimulatory peptides. The claims by Stanley et al. clearly state that the expression vector encode at least one papillomavirus protein, clearly encompassing multiple expression vectors, each expressing a different papillomavirus protein that **are not fused** to each other, see page 6, line 7 and page 11, lines 21-25. In addition, Stanley et al. teaches that the composition is injected, see page 6, lines 28-31 and page 7, lines 7-15. All of the teachings of Stanley et al. anticipate claims 38, 39, 41-48, 50, 58-60, 62-64, 66, 74-76, and 78.

Furthermore, while Stanley et al. does not contain a working example with the specific combinations of the early and late regions in the papillomavirus in claims 6, 8, 15, or 17, the claims of Stanley et al. are directed to the "...at least one of proteins E6, E7, L1, **and**/or L2...", which includes this combination of the papillomavirus proteins.

Applicants argue in response to the previous rejection that the teachings of Stanley et al. cannot be broadened to encompass the use of non-IL-12 immunostimulatory molecules and that by this observation, every single element was not taught by the reference. This argument is not

found convincing because the claims are drawn to treatment or prevention using papillomavirus peptides and a polypeptide having an immunostimulatory activity, which encompasses IL-12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40, 49, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al.

Although the teachings of Stanley et al. do not include non-oncogenic variants of the peptides claimed in the instant application, it is clearly suggested that the peptides and antigenic fragments taught by Stanley et al. are non-oncogenic because any peptide that would not treat papillomavirus infections and would cause antigenic legions would be excluded from the teachings of Stanley et al. Also, Stanley et al. teaches "...the substantial part of the sequence ..." of E6, E7, L1, and/or L2 in claims 6-8 and 14-17, would anticipate the instant application in claiming a sequence homology that has a similarity greater than 75% with the papillomavirus proteins. Therefore, the non-oncogenic variants of the papillomavirus proteins in claims 40, 49, and 64 are rendered obvious by the teachings of Stanley et al.

Claims 38-55 and 58-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Galloway, Hines et al., and Gajewski.

The claims are drawn to a pharmaceutical composition intended for the treatment or prevention of a papillomavirus infection, tumor, and dysplasia that comprises nononcogenic

polypeptides that is from the early region and a polypeptide that is a from the late region of the papillomavirus. The early proteins are E6 and/or E7 and L1 and/or L2 derived from human papillomaviruses. In addition, the composition is contains an immunostimulatory peptide, such as IL-1, IL-7, B7.1, and B7.2.

Galloway teaches a prospect for prophylactic vaccine to treat papillomavirus infections with a composition that includes L1and L2 proteins and therapeutic vaccines that include E6 and E7 proteins from the papillomavirus, see the abstract on page 187. Rabbits immunized with L1 or L2 conferred protective immunity against the virus, see first full paragraph of column 2 on page 190. E7 was found to protect mice from a syngeneic tumor in a MHC-restricted fashion, see the paragraph bridging pages 190-191. Stimulation of the immune response against E6 and/or E7 may be beneficial in clearing tumors, see the next to the last sentence of the second column on page 191. From the teachings of Galloway, one of skill in the art at the time of the invention would have been motivated to combine E6, E7, L1, and/or L2 into a vaccine to treat or prevent a papillomavirus infection. One of skill in the art at the time of the invention would have had a reasonable expectation of success because of the prophylactic properties of L1 and L2 to confer immunity and the treatment of tumors demonstrated by E6 and E7. Galloway does not teach injecting the vaccine. However, vaccination is by injection is a conventional form of administration in the art. Galloway does not teach the use of IL-2 and B7.1 to aid in activating the immune response.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the response to the previous Office action, the Applicants argued that Galloway does not teach immunostimulatory peptides. It was noted in the original 103 rejection that the reference does not teach that limitation, which is why the reference was combined with one that did teach that limitation.

Applicants also argued that one teaching by Galloway was the E7 and L2 combination was found inefficient in therapy and that the reference does not provide a motivation to put the early and late polypeptides together to treat papillomavirus infections. Applicants' attention should be drawn to the fact that Galloway teaches that Galloway teaches the general characteristics of the late proteins, L1 and L2 to have prophylactic capabilities and early proteins, E6 and E7, to be therapeutic, see the abstract, the full paragraph on the second column on page 190 and the next paragraph bridging page 191. One of skill in the art at the time the invention was made would have been motivated to combine the therapeutic effects of the early proteins and the prophylactic effects of the late proteins in order to treat patients, regardless of whether they were already infected or needed to prevent infection. Although the Applicants' arguments have been considered, the rejection is maintained.

Applicant states that the references fail to teach that the action of the immunostimulatory molecule to enhance the protective effect conferred by the papilloma polypeptides and that the teachings of IL-2 and B7.1 by Hines et al. and Gajewski are used to induce the proliferation of naïve lymphocytes to activate a cytotoxic phenotype. Applicants are reminded that the claims are drawn to a pharmaceutical composition intended for the treatment **or** prevention of a

papillomavirus infection. The references teach that stimulation of the immune response can be accomplished by injecting IL-2 (Hines et al.) or B7.1 (Gajewski) to stimulate T cells. Thus, the teachings of the references specifically teach the limitations not taught by Galloway.

Claims 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Galloway, Hines et al., and Gajewski as applied to claims 38-55 and 58-78 above, and further in view of Munger et al. and Crook et al.

Applicants have argued that the teachings of Galloway, Hines et al., and Gajewski do not render the claimed invention obvious, so the combination of Crook et al. and Munger et al. do not render the invention obvious.

However, Applicant's arguments regarding Galloway, Hines et al., and Gajewski are unconvincing, see above. Therefore, it is maintained that the teachings of Crook et al. and Munger et al. render the invention as a whole prima facie obvious to one of skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
March 2, 2001

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1600